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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/918,601 | 07/30/2001 | Garry P. Nolan | A-64260-5/DJB/RMS/AMS | 6631 |

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| EXAMINER | |
|---|---|
| WESSENDORF, TERESA D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1639 | |

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/918,601 | NOLAN, GARRY P. | |
| | Examiner | Art Unit | |
| | T. D. Wessendorf | 1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *23-26,28-30,32,34-37,40-52 and 54-57* is/are pending in the application.

4a) Of the above claim(s) *23,28,30,40-42,47-52 and 54-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-26,29,32,34-37 and 43-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/23/04 has been entered.

### *Election/Restrictions*

Applicant's election with traverse of Group II, species c, i.e., targeting sequence is acknowledged. The traversal is on the ground(s) that the subject matter of several of the claim groups is completely encompassed by the other claim groups. For example, applicant submits that claim 24 (Group II) is generic to both claim 28 (Group III) and claim 29 (of Group lV). Applicant respectfully submits that there is no basis for this restriction requirement. This is not found persuasive because Group III is drawn to a distinct and different invention comprising of peptide with stop codon. However, in view of applicants' admission that Group II is generic to Group IV, the

restriction between these two Groups has been reconsidered. Group IV will be examined with the elected Group II.

The requirement is still deemed proper and is therefore made FINAL.

***Status of Claims***

Claims 1-22, 27, 31, 33, 38-39, 53 and 58 have been cancelled.

Claims 23-26, 28-30, 32, 34-37, 40-52 and 54-57 are pending.

Claims 23, 28, 30, 40-42, 47-52 and 54-57 are withdrawn from consideration as being drawn to non-elected invention and species.

Claims 24-26, 29, 32, 34-37 and 43-46 are under examination.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 47-52 and 54-57 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter and lacks patentable utility.

In view of the election of Group II, i.e., method claims, these claims (47-52 and 54-57) have been withdrawn from consideration. Hence, the rejection under the 101 statutes no longer applies.

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-26, 29, 32, 34-37 and 43-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific library as provided in Figs. 1 and 2 (Example 2), a tumor cell and other specific embodiments disclosed in the specification does not reasonably provide enablement for the broadly claimed variables encompassed by the claimed method and library for reasons set forth in the last Office action.

***Response to Arguments***

Applicants argue that on page 19, line 30 to page 20, line 9 the specification discloses that the candidate bioactive agents and candidate nucleic acids are randomized, either fully randomized or they are biased in their randomization, e.g. in nucleotide/residue frequency generally or per position. By

"randomized" or grammatical equivalents herein is meant that each nucleic acid and peptide consists of essentially random nucleotides and amino acids, respectively. As is more fully described below, the candidate nucleic acids, which give rise to the candidate expression products, are chemically synthesized.

In response, it is not the definition of the candidate bioactive peptide that is at issued. Applicants recognized that the definition is known to a skilled artisan. The issue herein is the randomization of a molecular library of 104 undefined retroviral nucleic acid that encodes 4 to 100 amino acids. For example, it is not apparent from the broad description the residues in the peptide sequence that is randomized, the length of the random residues and the biased residues, the location and the kind of random sequences. Are all the residues in the library of the same (e.g., all are four residues) or different for the 104 different retroviral nucleic acid sequences? What about the random portions? This library is but only one of the numerous undefined components of the broad method. A skilled in the art still needs to consider, after the making of this random library, its introduction into the appropriate cell(s) such that the members in the library are truly represented in the library, its interaction with any class of molecules and the screening

method that would result in a peptide that is transdominant and intracellularly present in the cell.

Most of applicants' arguments are drawn to the different embodiments of the invention. For example, it is argued that the specification provides substantial detail and guidelines for he composition of fusion partners for the randomized sequence. Where the fusion partner is a presentation structure, the structures are stated to include minibody structures, loops on beta sheet turns and etc. (page 7, lines 14-16). It is argued that the specification provides for the suitable targeting sequence at e.g., page 9, lines 15-24. See the REMARKS at page 12. Applicants conclude that it is not required that applicant provide a working exemplification for every embodiment of a claim nor to spell out every detail. A patent specification is not intended nor required to be a production specification.

In reply, the specification will only become a production specification when it presents only a list of a general component and general embodiments of the generic claims. As apparent from applicant's REMARKS and specification, there are several embodiments of the claimed invention each encompassing different inventions. The broad recitation of these embodiments does not translate to an enabling disclosure for the broad invention. Because of the high unpredictability of the peptide

art, let alone, the library, a priori statement has never been made in the art. Applicant recognized and admits that it is well known in the art that **protein expression is dependent on the host cell, expression vector, regulatory elements,** etc. The literature provides ample guidance for selecting the **appropriate combination of elements and vectors** (and not any elements as generically claim). The teachings in the literature are specific for specific combinations of elements. As further admitted by applicant, protein expression is dependent on host cell. That is, the host cell will express only components that do not deleteriously affect its function or expression. Or will express the components in a library that would be representative of the compounds therein. The claims as broadly written, does not take this into account. Attention is also drawn to Wetters et al at page 554, col. 1 as to the their statement that "…observed ambiguities in sequences …were so numerous as to prevent...from drawing even tentative conclusions about mutations responsible for transformation….."

Applicant is not required to test each and every compounds provided in the list. Rather, that the specification provides reasonable assurance that the single embodied components is a sufficient enabling disclosure for the broad scope of the claims.

In a highly undeveloped and unexplored art as gene technology, usually experimental examples provide guidance to the applicability to the broad generic method, as claimed.

As stated in the last Office action, there are far too numerous factors to determine for the successful practice of the claimed invention. A priori statement as to the applicability of a specifically defined factor, to date, has not been made to broad claims as the instant claims.

[As suggested in the last Office action, this rejection can be obviated by reciting method steps as disclosed in Figs. 1 and 2 with the specific biased random library of nucleic acid and tumor cells].

***Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 34-37, 40 and 43-46, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). These claims improperly depend on the non-elected claim 23.

***Double Patenting***

Claims 24-26, 29, 32, 34-37 and 43-46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,365,344('344 Patent) for reasons of record.

Applicant argues that the '344 Patent requires that the peptides comprise a section signal sequence which is not native to a first plurality of mammalian cells and act on a second cell second plurality of mammalian cells to generate a changed physiology in response to a transdominant bioactive peptide expressed by the first plurality of mammalian cells. It is argued that the present invention screen for peptides that act on the cells in which they are expressed and the claims recite specific sequence variations not taught in the claims of the '344 Patent.

In response, whether the transdominant peptide uses a first and/or second cells as in the '344 Patent would have been obvious as there is no differentiation of a first and second cell in said '344 patent. The first and second cell could very well be similar, if not the same, as the resultant effect of the peptide of causing phenotypic changes is obtained. Furthermore, claim 24 does not recite for the argued specific sequence

variations. Nevertheless, this species would be encompassed by the broad claimed peptide of the '344 Patent.

***Claim Rejections - 35 USC § 103***

Claims 24-26, 29, 32, 34-37 and 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al (USP 6,703,482) in view of Williams (USP.

Kay et al discloses at e.g., col. 8, line 19 up to col. 12, line 34 a method is provided of identifying a peptide having a region that binds to an SH3 domain comprising: (a) providing an immobilized target protein comprising an SH3 domain; (b) incubating the immobilized target protein with an aliquot taken from a phage-displayed random peptide library, which library includes peptides having a random sequence of 8 amino acid residues; (c) washing unbound phage from the immobilized target protein; (d) recovering the phage bound to the immobilized target protein; and (e) determining the relevant nucleotide sequence of said binding phage nucleic acid and deducing the primary sequence corresponding to the SH3 domain-binding peptide. Kay discloses that the random peptides have at least nine and up to forty-five amino acid residues, including an amino acid sequence of the formula, R-2-L-P-5-6-P-8-9 (SEQ ID

NO:10), positioned anywhere along the peptide, in which each number represents an amino acid residue, such that 2 represents any amino acid residue except cysteine, 5 and 6 each represents a hydrophobic amino acid residue, 8 represents any amino acid residue except cysteine, and 9 represents a hydrophilic amino acid residue except cysteine. The peptides also exhibit a binding affinity for the SH3 domain of Src-related proteins, including Yes, Fyn, Lyn, Lck, Hck and Fgr.

Kay discloses at e.g., that Any other mode by which the peptide library, random or otherwise, can be "displayed" can be utilized. A longer random peptide sequences (e.g., >6 amino acid residues, preferably >10, and most preferably, >12) provide not only much greater diversity but also a richer degree of secondary structure conducive to binding activity. The preparation of the random peptide library is described at e.g., The libraries have approximately greater than 108 different recombinants, and nucleotide sequencing of the inserts suggests that the expressed peptides are indeed random in amino acid sequence. Kay discloses that transformed host cells are also obtained by the methods of the present invention which are capable of reproducing the polynucleotide sequences of interest and/or expressing the corresponding peptide products. A variety of hosts including prokaryotic and eukaryotic hosts are

disclosed. In particular, bacterial, viral, yeast, animal, and plant cells are potentially transformable hosts. Thus, a method is disclosed to obtain a transformed host cell that can produce, preferably secrete, a peptide having a region that binds to an SH3 domain comprising (a) providing an expression vector, preferably a secretory expression vector, comprising a nucleotide sequence encoding at least one copy of a peptide having a region that binds to an SH3 domain; and (b) introducing the vector to a competent host cell.

Kay does not disclose the use of retroviral nucleic acid (vector) in the method and the targeting sequences i.e., myristylation sequence. However, Williams discloses at e.g., the abstract that recombinant viral vectors efficiently transfer and precisely and stably integrate exogenous DNA into cellular DNA of host cells such as animal cells, particularly mammalian cells. It is well known in the art that this allows prolonged or repeated rounds of phenotypic screening. Crabtree discloses at e.g., the abstract that fusion proteins have a binding domain for binding to the (preferably small) organic oligomerizing molecules and an action domain, which can effectuate a physiological action or cellular process as a result of oligomerization of the chimeric proteins. See Fig. 21 B which discloses the myristolylation sequence.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use in the method of Kay a retroviral vector for its advantages as taught by Williams and provide for a fusion protein as taught by Crabtree. This advantage taught by Williams and Crabtree would provide the motivation to one having ordinary skill in the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
April 19, 2004

No claim is allowed.